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EXAMINER	
ROMEO, DAVID S	
ART UNIT	PAPER NUMBER
1647	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	08/945,459	MAKISHIMA ET AL.	
	Examiner	Art Unit	
	David S Romeo	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 May 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *49-66* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *49-66* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 02/17/2004 has been entered.

Claims 49-66 are pending and being examined.

New Formal Matters, Objections, and/or Rejections:

Claim Rejections - 35 USC § 103

Claim 49 is rejected under 35 U.S.C. 103(a) as being unpatentable over {Celeste (A, Paper No. 10), Ben-Bassat (W, Paper No. 10), and Hirel (U, Paper No. 20)} in view of Georgiou (X, Paper No. 13).

Celeste teaches mature MP52 containing the amino acid sequence of Celeste's SEQ ID NO: 4 (column 3, lines 51-52). Amino acids #2 to #120 of Celeste's SEQ ID NO: 4 are identical to applicants' SEQ ID NO: 1. Celeste teaches that the first cysteine of the seven cysteine domain of MP52 is encoded by the codon beginning at nucleotide #899 of Celeste's SEQ ID NO: 3 (column 7, full paragraph 3). The codon beginning at nucleotide #899 of Celeste's SEQ ID NO: 3 encodes amino acid #19 of Celeste's SEQ ID NO: 4. Celeste teaches human MP52 proteins containing the amino acid sequence from amino acid #17 or #19 to #119 or #120 of Celeste's SEQ ID NO: 4 are expected to retain activity (column 7, full paragraph 3). Celeste teaches that

the MP52 protein appears to begin at nucleotide 845 off Celeste's SEQ ID NO: 3 and continues through nucleotide 1204 of Celeste's SEQ ID NO: 3 (column 7, full paragraph 2). Celeste teaches that purified MP52 proteins may be produced by culturing a host cell transformed with a DNA sequence of Celeste's SEQ ID NO: 3 from nucleotide 845 to 1204 (column 7, full paragraph 3). Bacterial cells may also be suitable hosts (paragraph bridging columns 8-9) and the bacterially expressed MP52 can be isolated using techniques that are well known in the art (column 9, full paragraph 1). In expressing mature MP52 (Celeste's SEQ ID NO: 4) in a bacterial host one would use a DNA molecule encoding MP52 with the N-terminal sequence Met-Ala-Pro-. Celeste is silent with respect to a protein consisting of the 119 amino acids as shown in SEQ ID NO: 1, wherein said protein is free of proteins with an Ala- or Met-Ala- at the N-terminus.

Ben-Bassat teaches that in the case of Met-Ala-Pro-IL2, 60% of the bacterially expressed protein also lost the alanine residue, while no alanine removal was detected from the in vitro methionine aminopeptidase (MAP) reaction. Ben-Bassat suggest that another aminopeptidase(s) might be responsible for the removal of the alanine residue. See page 755, paragraph bridging columns 1-2. Ben-Bassat also suggest obtaining a homogeneous protein product without the N-terminal methionine; purified MAP could be used to "polish" the frayed amino terminal sequences (page 756, paragraph bridging columns 1-2).

Hirel, like Ben-Bassat, using a Met-Ala-Pro-Val-hybrid protein also observed that proline in the third position inhibited MAP action. However, the catalytic efficiency of MAP was insensitive to a Met-Pro- sequence. Furthermore, at least 6.5% of the processed Met-Ala-Pro-Val-hybrid protein had also lost the second Ala residue. Page 8250, column 2, full paragraph 4.

In expressing Celeste's mature MP52 in bacteria one of ordinary skill in the art would reasonably expect to obtain mature MP52 with the following N-terminal amino acid sequences, according to the teachings of Ben-Bassat and Hirel: Met-Ala-Pro, Ala-Pro, and Pro. The mature MP52 with a Pro at the N-terminus is identical to the claimed protein consisting of the 119 amino acids as shown in SEQ ID NO: 1. One of ordinary skill in the art would be motivated to express mature MP52 in bacteria because gene cloning and expression in bacteria would provide an abundant source of readily purified protein.

Celeste, Ben-Bassat, and Hirel do not teach a protein consisting of the 119 amino acids as shown in SEQ ID NO: 1, wherein said protein is free of proteins with an Ala- or Met-Ala- at the N-terminus.

Georgiou teaches that the production of proteins that are identical to the natural product are highly desirable in the pharmaceutical industry, that the difference of a single amino acid residue can be deleterious to a patient receiving the protein and complicates approval of the product by the FDA (page 1240, paragraph bridging columns 1-2). Georgiou does not teach a protein consisting of the 119 amino acids as shown in SEQ ID NO: 1, wherein said protein is free of proteins with an Ala- or Met-Ala- at the N-terminus.

However, it would have been obvious to one of ordinary skill in the art at the time of Applicants' invention to express Celeste's mature MP52 in bacteria, to isolate the bacterially expressed protein therefrom, and to obtain a mixture of Met-Ala-Pro-MP52, Ala-Pro-MP52, and Pro-MP52, as taught by Celeste, Ben-Bassat, and Hirel, and to modify that teaching by "polishing" the frayed amino terminal sequence with purified MAP, as taught by Ben-Bassat, with a reasonable expectation of success. One of ordinary skill in the art would be motivated to

make this modification because Met-Ala-Pro-MP52 is not identical to the natural product, Ala-Pro-MP52 and Pro-MP52 are identical to the natural product, and the natural product is highly desirable in the pharmaceutical industry, and the difference of a single amino acid residue can be deleterious to a patient receiving the protein and complicates approval of the product by the FDA. Following the teachings of Celeste, Ben-Bassat, and Hirel in view of Georgiou on would obtain a protein consisting of the 119 amino acids as shown in SEQ ID NO: 1, wherein said protein is free of proteins with a Met-Ala- at the N-terminus.

The claimed product is claimed in part in a product-by-process format. The references do not describe the production of the claimed product using methods identical to that recited in claim 49. However, the recitation of a process limitation in claim 49 is not viewed as positively limiting the claimed product absent a showing that the process of making recited in claim 49 imparts a novel or unexpected property to the claimed product, as it is assumed that equivalent products are obtainable by multiple routes. The burden is upon the applicants to establish a patentable distinction between the claimed and referenced products.

The invention is prima facie obvious over the prior art.

Claim 49 is rejected under 35 U.S.C. 103(a) as being unpatentable over [{Celeste (A, Paper No. 10), Ben-Bassat (W, Paper No. 10), and Hirel (U, Paper No. 20)} in view of Georgiou (X, Paper No. 13)] and further in view of Thompson (A, Paper No. 27) and Tonouchi (Y, Paper No. 13).

Celeste, Ben-Bassat, and Hirel in view of Georgiou teach an isolated protein consisting of the amino acid sequence of SEQ ID NO: 1 and an isolated protein consisting of the amino acid

sequence of SEQ ID NO: 1 with an Ala- at the N-terminus, as discussed above. That is to say that Celeste, Ben-Bassat, and Hirel in view of Georgiou teach a protein consisting of the 119 amino acids as shown in SEQ ID NO: 1, wherein said protein is free of proteins with a Met-Ala- at the N-terminus.

Celeste, Ben-Bassat, and Hirel in view of Georgiou do not teach a protein consisting of the 119 amino acids as shown in SEQ ID NO: 1, wherein said protein is free of proteins with an Ala- at the N-terminus.

Thompson teaches that it is generally considered desirable for clinical use to obtain a homogeneous material, i.e. a protein having essentially the same N-terminal sequence from molecule to molecule (paragraph bridging columns 1-2).

Tonouchi teaches the removal of an N-terminal Ala with aminopeptidase P (Figure 3). The digestion was performed completely (page 33, paragraph bridging columns 1-2). The examiner has interpreted the term "performed completely" to indicate that the mature BSF-2 was without residual proteins.

Thompson and Tonouchi do not teach a protein consisting of the 119 amino acids as shown in SEQ ID NO: 1, wherein said protein is free of proteins with an Ala- at the N-terminus.

However, it would have been obvious to one of ordinary skill in the art at the time of Applicants' invention to make a protein consisting of the 119 amino acids as shown in SEQ ID NO: 1, wherein said protein is free of proteins with a Met-Ala- at the N-terminus, as taught by Celeste, Ben-Bassat, and Hirel in view of Georgiou, and to modify that teaching by completely digesting the N-terminal Ala with aminopeptidase P, as taught by Tonouchi, with a reasonable expectation of success. One of ordinary skill in the art would be motivated to make this

modification because it is generally considered desirable for clinical use to obtain a homogeneous material, i.e. a protein having essentially the same N-terminal sequence from molecule to molecule. In so doing one would obtain an isolated protein consisting of the amino acid sequence of SEQ ID NO: 1, wherein said protein is free of proteins with an Ala- and a Met-Ala- at the N-terminus.

The invention is prima facie obvious over the prior art.

Claims 49, 50 are rejected under 35 U.S.C. 103(a) as being unpatentable over [{Celeste (A, Paper No. 10), Ben-Bassat (W, Paper No. 10), and Hirel (U, Paper No. 20)} in view of Georgiou (X, Paper No. 13)] and further in view of Thompson (A, Paper No. 27) and Tonouchi (Y, Paper No. 13) as applied to claim 49 above and further in view of Hotten (2, cited by Applicants) and Cerletti (N, Paper No. 10).

Celeste, Ben-Bassat, and Hirel in view of Georgiou and further in view of Thompson and Tonouchi teach an isolated protein consisting of the amino acid sequence of SEQ ID NO: 1, wherein said protein is free of proteins with an Ala- and a Met-Ala- at the N-terminus, as discussed above. Celeste, Ben-Bassat, and Hirel in view of Georgiou and further in view of Thompson and Tonouchi are silent with respect to said protein being a homodimer.

Hotten teaches that native GDF-5 is a dimer of the disulfide linked mature part of the protein as is seen in other TGF-β family members (page 650, first paragraph of discussion). GDF-5 is MP52.

Cerletti teaches a process for the production of biologically active, dimeric, mature TGF-β-like proteins. The process comprises culturing an E. coli host that has been transformed with a

plasmid containing DNA encoding the amino acid sequence of a mature TGF-β-like protein (page 7, lines 9-14 and lines 40-41), solubilizing inclusion bodies obtained by culturing said E. coli, purifying the monomer protein from the solubilized solution, refolding the monomer protein into a dimer protein, and purifying same (page 7, line 56 through page 8, line 15).

Hotten and Cerletti do not teach an isolated protein consisting of the amino acid sequence of SEQ ID NO: 1, wherein said protein is free of proteins with an Ala- and a Met-Ala- at the N-terminus.

However, it would have been obvious to one of ordinary skill in the art at the time of Applicants' invention to make an isolated protein consisting of the amino acid sequence of SEQ ID NO: 1, wherein said protein is free of proteins with an Ala- and a Met-Ala- at the N-terminus, as taught by Celeste, Ben-Bassat, and Hirel in view of Georgiou and further in view of Thompson and Tonouchi, and to modify that teaching by forming native biologically active dimers, as taught by Hotten and Cerletti, with a reasonable expectation of success. One of ordinary skill in the art would be motivated to combine these teachings in order to form the native, biologically active form of the protein.

The invention is prima facie obvious over the prior art.

Claims 49-60, 63, 66 are rejected under 35 U.S.C. 103(a) as being unpatentable over [{Celeste (A, Paper No. 10), Ben-Bassat (W, Paper No. 10), and Hirel (U, Paper No. 20)} in view of Georgiou (X, Paper No. 13)] and further in view of Thompson (A, Paper No. 27) and Tonouchi (Y, Paper No. 13) as applied to claim 49 above and further in view of Hotten (2, cited

by Applicants) and Cerletti (N, Paper No. 10) as applied to claims 49, 50 above and further in view of Neidhardt (1, cited by Applicants).

Celeste, Ben-Bassat, and Hirel in view of Georgiou and further in view of Thompson and Tonouchi and further in view of Hotten and Cerletti teach a homodimer of an isolated protein consisting of the amino acid sequence of SEQ ID NO: 1, wherein said protein is free of proteins with an Ala- and a Met-Ala- at the N-terminus, as discussed above. Celeste, Ben-Bassat, and Hirel in view of Georgiou and further in view of Thompson and Tonouchi and further in view of Hotten and Cerletti do not teach a pharmaceutical composition comprising a homodimer of an isolated protein consisting of the amino acid sequence of SEQ ID NO: 1, wherein said protein is free of proteins with an Ala- and a Met-Ala- at the N-terminus, in an amount effective to treat cartilage and/or bone disease in combination with a pharmaceutical carrier.

Neidhardt teaches a pharmaceutical composition comprising MP52 and a pharmaceutically acceptable carrier for use in the healing of bone, cartilage, or tooth defects (page 9, full paragraph 1). Neidhardt does not teach a homodimer of an isolated protein consisting of the amino acid sequence of SEQ ID NO: 1, wherein said protein is free of proteins with an Ala- and a Met-Ala- at the N-terminus.

However, it would have been obvious to one of ordinary skill in the art at the time of Applicants' invention to make a homodimer of an isolated protein consisting of the amino acid sequence of SEQ ID NO: 1, wherein said protein is free of proteins with an Ala- and a Met-Ala- at the N-terminus, as taught by Celeste, Ben-Bassat, and Hirel in view of Georgiou and further in view of Thompson and Tonouchi and further in view of Hotten and Cerletti, and to modify that teaching by making a pharmaceutical composition comprising pharmaceutically acceptable

carrier for use in the healing of bone, cartilage, or tooth defects, as taught by Neidhardt, with a reasonable expectation of success. One of ordinary skill in the art would be motivated to make this modification in order to make a composition suitable for the healing of bone, cartilage, or tooth defects. An amount effective to heal bone, cartilage, or tooth defects is an amount effective to treat the recited cartilage and/or bone diseases in the presently claimed compositions, in the absence of evidence to the contrary. The pharmaceutically acceptable carrier is suitable for local administration and suitable for coating onto the surface of cartilage, bone, or tooth in the absence of evidence to the contrary.

The invention is prima facie obvious over the prior art.

Claims 49-51, 64, 65 and claims 52-60, 63, 66 are rejected under 35 U.S.C. 103(a) as being unpatentable over [{Celeste (A, Paper No. 10), Ben-Bassat (W, Paper No. 10), and Hirel (U, Paper No. 20)} in view of Georgiou (X, Paper No. 13)] and further in view of Thompson (A, Paper No. 27) and Tonouchi (Y, Paper No. 13) as applied to claim 49 above and further in view of Hotten (2, cited by Applicants) and Cerletti (N, Paper No. 10) as applied to claims 49, 50 above and further in view of Neidhardt (1, cited by Applicants) as applied to claim 51 above and further in view of Hotten (A, Paper No. 37) and Chen (U. S. Patent No. 5707962). This rejection is also applied to claims 52-60, 63, 66 in the event that Applicants provide evidence that the pharmaceutically acceptable carrier in the immediately preceding rejection is NOT suitable for local administration and suitable for coating onto the surface of cartilage, bone, or tooth.

Celeste, Ben-Bassat, and Hirel in view of Georgiou and further in view of Thompson and Tonouchi and further in view of Hotten and Cerletti and further in view of Neidhardt teach a

pharmaceutical composition comprising a homodimer of an isolated protein consisting of the amino acid sequence of SEQ ID NO: 1, wherein said protein is free of proteins with an Ala- and a Met-Ala- at the N-terminus, in an amount effective to treat cartilage and/or bone diseases, in combination with a pharmaceutically acceptable carrier. Celeste, Ben-Bassat, and Hirel in view of Georgiou and further in view of Thompson and Tonouchi and further in view of Hotten and Cerletti and further in view of Neidhardt do not teach a pharmaceutical composition comprising a homodimer of an isolated protein consisting of the amino acid sequence of SEQ ID NO: 1, wherein said protein is free of proteins with an Ala- and a Met-Ala- at the N-terminus, in an amount effective to treat cartilage and/or bone diseases, in combination with a pharmaceutically acceptable carrier, wherein the pharmaceutical composition further comprises natural bone, metal, ceramic, glass, collagen, or hydroxyapatite.

Hotten discloses that in principle various matrix materials known to a person skilled in the art should be usable with MP52 (column 14, lines 4-5).

Chen discloses natural bone, metal, ceramic, glass, collagen, and hydroxyapatite matrix materials for use with osteoinductive factors (paragraph bridging columns 2-3).

Hotten and Chen do not teach a pharmaceutical composition comprising a homodimer of an isolated protein consisting of the amino acid sequence of SEQ ID NO: 1, wherein said protein is free of proteins with an Ala- and a Met-Ala- at the N-terminus, in an amount effective to treat cartilage and/or bone diseases, in combination with a pharmaceutically acceptable carrier.

However, it would have been obvious to one of ordinary skill in the art at the time of Applicants' invention to make a pharmaceutical composition comprising a homodimer of an isolated protein consisting of the amino acid sequence of SEQ ID NO: 1, wherein said protein is

free of proteins with an Ala- and a Met-Ala- at the N-terminus, in an amount effective to treat cartilage and/or bone diseases, in combination with a pharmaceutically acceptable carrier and to modify that teaching by substituting various matrix materials known to a person skilled in the art such as natural bone, metal, ceramic, glass, collagen, and hydroxyapatite matrix materials for use with osteoinductive factors, as taught by Hotten and Chen, with a reasonable expectation of success. One of ordinary skill in the art would be motivated to make this modification because various matrix materials known to a person skilled in the art such as natural bone, metal, ceramic, glass, collagen, and hydroxyapatite matrix materials are useful with osteoinductive factors. The various matrix materials are pharmaceutically acceptable carriers suitable for local administration and suitable for coating onto the surface of cartilage, bone, or tooth in the absence of evidence to the contrary.

The invention is prima facie obvious over the prior art.

Claims 49-51, 61, 62 are rejected under 35 U.S.C. 103(a) as being unpatentable over [{Celeste (A, Paper No. 10), Ben-Bassat (W, Paper No. 10), and Hirel (U, Paper No. 20)} in view of Georgiou (X, Paper No. 13)] and further in view of Thompson (A, Paper No. 27) and Tonouchi (Y, Paper No. 13) as applied to claim 49 above and further in view of Hotten (2, cited by Applicants) and Cerletti (N, Paper No. 10) as applied to claims 49, 50 above and further in view of Neidhardt (1, cited by Applicants) as applied to claim 51 above and further in view of Ron (U. S. Patent No. 5,171,579) and Avis (Avis, K.E. "Parenteral Preparations", Chapter 84, in, Remington's Pharmaceutical Sciences, 18th edition (June 1990), Mack Pub. Co., Easton, Pennsylvania).

The present specification discloses that injectable preparations can be formulated in the form of injectable powders. The powders can be prepared by adding one or more of suitable water-soluble excipients such as mannitol, sucrose, lactose, maltose, glucose, fructose and the like, to an active ingredient, dissolving the mixture in water, dividing it into vials or ampoules followed by lyophilizing and hermetically sealing. See page 7, full paragraph 2. Accordingly, a lyophilized preparation comprises a pharmaceutical carrier that is suitable for injection or an injectable powder.

Celeste, Ben-Bassat, and Hirel in view of Georgiou and further in view of Thompson and Tonouchi and further in view of Hotten and Cerletti and further in view of Neidhardt teach a pharmaceutical composition comprising a homodimer of an isolated protein consisting of the amino acid sequence of SEQ ID NO: 1, wherein said protein is free of proteins with an Ala- and a Met-Ala- at the N-terminus, in an amount effective to treat cartilage and/or bone diseases, in combination with a pharmaceutically acceptable carrier. Celeste, Ben-Bassat, and Hirel in view of Georgiou and further in view of Thompson and Tonouchi and further in view of Hotten and Cerletti and further in view of Neidhardt do not teach a pharmaceutical composition comprising a homodimer of an isolated protein consisting of the amino acid sequence of SEQ ID NO: 1, wherein said protein is free of proteins with an Ala- and a Met-Ala- at the N-terminus, in an amount effective to treat cartilage and/or bone diseases, in combination with a pharmaceutically acceptable carrier, wherein said pharmaceutical carrier is suitable for injection or an injectable powder.

Ron teaches that osteogenic proteins can be utilized in the form of a pharmaceutically acceptable solution (including reconstitution from a lyophilized form). It is optimal to solubilize

the osteogenic protein at concentrations of at least about 2 mg/ml, preferably about 4 mg/ml, so that a pharmaceutically effective amount of protein can be delivered without undue volumes of carrier being necessary (column 2, lines 22-29). Ron teaches that additional optional components useful in the practice of the subject application include, e.g. cryogenic protectors such as mannitol (to protect from degradation during lyophilization), preservatives, antioxidants, etc. (column 4, lines 45-48).

Avis teaches that the particular advantages of freeze-drying (lyophilization) are ease of processing a liquid, pharmaceuticals can be stored in a dry state in which there are relatively few stability problems, the products are often more soluble and/or more rapidly soluble, and dispersions are stabilized throughout their shelf-life (page 1565, paragraph bridging columns 1-2, through column 2, full paragraph 1). Avis teaches that mannitol has been found to be most useful to increase the solids content of the original solution to between approximately 5 and 25% so that the freeze-dried product plug occupies essentially the same volume as that of the original solution (page 1566, column 2, full paragraphs 1-3).

Ron and Avis do not teach a pharmaceutical composition comprising a homodimer of an isolated protein consisting of the amino acid sequence of SEQ ID NO: 1, wherein said protein is free of proteins with an Ala- and a Met-Ala- at the N-terminus, in an amount effective to treat cartilage and/or bone diseases, in combination with a pharmaceutically acceptable carrier.

However, it would have been obvious to one of ordinary skill in the art at the time of Applicants' invention to make a pharmaceutical composition comprising a homodimer of an isolated protein consisting of the amino acid sequence of SEQ ID NO: 1, wherein said protein is free of proteins with an Ala- and a Met-Ala- at the N-terminus, in an amount effective to treat

cartilage and/or bone diseases, in combination with a pharmaceutically acceptable carrier, as taught by Celeste, Ben-Bassat, and Hirel in view of Georgiou and further in view of Thompson and Tonouchi and further in view of Hotten and Cerletti and further in view of Neidhardt, and to modify that teaching by lyophilization, as taught by Ron and Avis, with a reasonable expectation of success. One of ordinary skill in the art would be motivated to make this modification because of ease of processing a liquid, pharmaceuticals can be stored in a dry state in which there are relatively few stability problems, the products are often more soluble and/or more rapidly soluble, and dispersions are stabilized throughout their shelf-life.

The invention is prima facie obvious over the prior art.

Claims 49-51, 60 are rejected under 35 U.S.C. 103(a) as being unpatentable over [{Celeste (A, Paper No. 10), Ben-Bassat (W, Paper No. 10), and Hirel (U, Paper No. 20)} in view of Georgiou (X, Paper No. 13)] and further in view of Thompson (A, Paper No. 27) and Tonouchi (Y, Paper No. 13) as applied to claim 49 above and further in view of Hotten (2, cited by Applicants) and Cerletti (N, Paper No. 10) as applied to claims 49, 50 above and further in view of Neidhardt (1, cited by Applicants) as applied to claim 51 above and further in view of Oppermann (U. S. Patent No. 5354557).

Celeste, Ben-Bassat, and Hirel in view of Georgiou and further in view of Thompson and Tonouchi and further in view of Hotten and Cerletti and further in view of Neidhardt teach a pharmaceutical composition comprising a homodimer of an isolated protein consisting of the amino acid sequence of SEQ ID NO: 1, wherein said protein is free of proteins with an Ala- and a Met-Ala- at the N-terminus, in an amount effective to treat cartilage and/or bone diseases, in

combination with a pharmaceutically acceptable carrier. Celeste, Ben-Bassat, and Hirel in view of Georgiou and further in view of Thompson and Tonouchi and further in view of Hotten and Cerletti and further in view of Neidhardt are silent with respect to a pharmaceutical composition comprising a homodimer of an isolated protein consisting of the amino acid sequence of SEQ ID NO: 1, wherein said protein is free of proteins with an Ala- and a Met-Ala- at the N-terminus, in an amount effective to treat cartilage and/or bone diseases, in combination with a pharmaceutically acceptable carrier, wherein the pharmaceutical carrier is suitable for systemic administration.

Oppermann discloses that osteogenic protein preparations in physiological saline may also be vortexed with the matrix and lyophilized to produce osteogenically active material (column 56, full paragraph 3). Oppermann does not teach a pharmaceutical composition comprising a homodimer of an isolated protein consisting of the amino acid sequence of SEQ ID NO: 1, wherein said protein is free of proteins with an Ala- and a Met-Ala- at the N-terminus, in an amount effective to treat cartilage and/or bone diseases, in combination with a pharmaceutically acceptable carrier, wherein the pharmaceutical carrier is suitable for systemic administration.

However, it would have been obvious to one of ordinary skill in the art at the time of Applicants' invention to make a pharmaceutical composition comprising a homodimer of an isolated protein consisting of the amino acid sequence of SEQ ID NO: 1, wherein said protein is free of proteins with an Ala- and a Met-Ala- at the N-terminus, in an amount effective to treat cartilage and/or bone diseases, in combination with a pharmaceutically acceptable carrier, as taught by Celeste, Ben-Bassat, and Hirel in view of Georgiou and further in view of Thompson

and Tonouchi and further in view of Hotten and Cerletti and further in view of Neidhardt, and to modify that teaching by substituting saline, as taught by Oppermann, with a reasonable expectation of success. One of ordinary skill in the art would be motivated to make this modification in order to produce osteogenically active material. A preparation in physiological saline is suitable for systemic administration in the absence of evidence to the contrary.

The invention is prima facie obvious over the prior art.

Claim Rejections - 35 USC § 112

Claims 49-66 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 49-66 are indefinite over the recitation of "an Ala, or Met and Ala at the N-terminus" (claim 49) because it is unclear if the protein lacks only a Met or Ala at the N-terminus or if it lacks an Ala, a Met, or a Met-Ala at the N-terminus. It is suggested that the claim recite "an Ala and a Met-Ala at the N-terminus."

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground

provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claim 49 is provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 14 of copending Application No. 09701121, which has been allowed but has not issued. Although the conflicting claims are not identical, they are not patentably distinct from each other because a "monomer MP52 protein comprising the amino acid sequence as shown in SEQ ID No: 2" (claim 14) encompasses an "isolated protein consisting of ... SEQ ID NO: 1, ... at the N-terminus" (claim 49).

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented. When the co-pending application issues the present rejection will become a double patenting rejection.

Claim 49 is provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 4 of copending Application No. 10751451. Although the conflicting claims are not identical, they are not patentably distinct from each other because a "monomer protein comprising an amino acid sequence described in SEQ ID No: 2" (claim 4) encompasses an "isolated protein consisting of ... SEQ ID NO: 1, ... at the N-terminus" (claim 49).

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 49-66 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-7 of copending Application No. 10365231. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the co-pending application are generic to and encompass the claims of the present application.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Devlin (Gene. 1988 May 15;65(1):13-22) discloses that because the N-terminal Met was not removed from G-CSF with the sequence Met-Thr-Pro-Leu-Gly-Pro-, they constructed a G-CSF expression vector in which the codon for Thr in the second position was deleted. The protein produced was sequenced and the N-terminal sequence was found to begin with Pro-Leu-Gly-Pro-. No detectable N-terminal Met was present. The methionine aminopeptidase is able to remove the methionyl residue from the Met-Pro-Leu-Gly-Pro- version of G-CSF, but not from the Met-Thr-Pro-Leu-Gly-Pro- version. See paragraph bridging pages 20-21.

No claims are allowable.

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JULY 29, 2004